II. The Claims Are Not Obvious Under 35 U.S.C. § 103

A. Claims 27, 34-36, 38, 40, 41, and 48-49 Are Patentable Over French in View of Mullenbach

Claims 27, 34-36, 38, 40, 41, and 48-49 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,290,949 to French *et al.* ("French") in view of Mullenbach *et al.*, UCLA Symp. Mol. Cell. Biol., New Ser., 82:313-326 (1988) ("Mullenbach".) (Office Action, pages 2-3.) Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the Office must demonstrate that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings. In the present case, the Office has failed to make a *prima facie* case of obviousness because at least this criterion has not been met.

The suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Furthermore, the Office has the burden to provide some objective evidence, not found in the Applicants' specification, or reasoned argument showing that one of ordinary skill in the art would have been motivated to combine the prior art to devise the claimed invention. *In re Lee*, 277 F.3d 1338, 1433 (Fed. Cir. 2002).

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness because there simply is no clear and particular suggestion in the cited

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

references to combine the adenoviral vector of French with Mullenbach's cDNA encoding glutathione peroxidase. The Office previously admitted that French "does not explicity teach using a sequence encoding a human glutathione peroxidase," and that Mullenbach teaches "the cDNA sequence [of] human glutathione peroxidase." (Office Action mailed on June 24, 2002, page 3.) From this evidence the Office concludes that one of ordinary skill in the art would have been motivated to combine these references:

> [C]ommon sense dictates that if one is gong to introduce a gene into an organism to supplement or overcome a deficiency, that one use the gene endogenous to that species, in this case the human glutathione peroxidase. ... Consider the obverse, why would one of skill in the art choose to deliver a bovine glutathione peroxidase DNA to a human patient if the human DNA was known.

(*Id.*) Applicants submit that the Office's conclusion that "common sense dictates that if one is going to introduce a gene into an organism to supplement or overcome a deficiency, that one use the gene endogenous to that species" is not based upon sufficient objective evidence or a reasoned argument showing that one of ordinary skill in the art would have been motivated to combine the cited references. For example, French provides only general guidance as to which of the many possible "therapeutic gene sequences" cited therein to choose from (for example, col. 7, line 58, to col. 8, line 26), and provides no guidance regarding relative advantages of human glutathione peroxidase genes over bovine glutathione peroxidase genes. Further, the Office's unsupported supposition that "one of skill in the art [would not] choose to deliver a bovine glutathione peroxidase DNA to a human patient if the human DNA was known" is not evidence that there was motivation at the time of filing to combine or modify French with the cDNA of Mullenbach.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Also, the Office asserts that "applicant has not challenged that one of ordinary skill in the art was not aware of the potential for immune response against a foreign therapeutic gene..." Office Action, page 3. Applicants point out that the Office's statement that "one of ordinary skill in the art was not aware of the potential for immune response against a foreign therapeutic gene..." is inconsistent with its argument that such alleged knowledge would provide motivation to combine the references to devise the claimed invention. Further, the mere fact that references can be combined does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Here, Applicants submit that the cited references do not suggest the desirability of combining the adenoviral vectors of French with the cDNA of Mullenbach. The only motivation to combine the references and derive the claimed invention comes from the Applicants' own specification.

In view of these remarks, Applicants respectfully request that the Office reconsider and withdraw the rejection.

B. Claims 27, 34-36, 38, 40, 41, and 48-50
Are Patentable Over Ohya in View of McClelland

Claims 27, 34-36, 38, 40, 41, and 48-450 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,187,078 to Ohya *et al.* ("Ohya") in view of U.S. Patent No. 5,543,328 to McClelland *et al.* ("McClelland".) (Office Action, pages 3-4.) Applicants respectfully traverse this rejection for reasons of record and as supplemented below. The Office has failed to establish a *prima facie* case of obviousness because there is no motivation to combine the references since there simply is no clear and particular suggestion in the cited references to

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

combine Ohya's plasmid encoding a glutathione peroxidase with McClelland's recombinant adenoviral vector.

In response to Applicants' arguments filed November 25, 2002, the Office asserts that the Applicant is arguing against the references individually "where the rejections are based on combinations of references. Office Action, pages 3-4. Applicants, however, point out that to establish a *prima facie* case of obviousness, the Office must demonstrate that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings. *See* M.P.E.P. § 2143. Applicants' argument below indicates that the references individually, and taken together, lack evidence of motivation to combine them to devise the claimed invention.

The Federal Circuit has made it clear that a rejection under section 103 cannot rely on reasoning that "presents, in essence, an 'obvious to experiment' standard for obviousness." *In re Dow Chemical Co. v. American Cyanamid Co.,* 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Such a standard "would not only be contrary to statute but result in a marked deterioration of the entire patent system..." *In re Thomlinson*, 150 U.S.P.Q. 623, 626 (C.C.P.A. 1966).

The Federal Circuit has given some examples of what would constitute an "obvious to experiment" or "obvious to try" modification based on the prior art:

> In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

> the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

(*In re O'Farrell*, 7 U.S.P.Q.2d 1673 at 1681 (Fed. Cir. 1988) (citations omitted) (emphasis added).)

The Office's rationale for combining Ohya and McClelland appears to be based upon an impermissible selective "picking and choosing" of specific components. The Office has admited that Ohya "does not teach [making] a replication deficient adenoviral vector for this purpose" and then concludes:

> [I]t would have been obvious to one of ordinary skill in the art to have made an adenoviral vector of McClelland *et al.* carrying the gene encoding the human glutathione peroxidase of Ohya *et al.* for transfecting cultured mammalian cells for the production of the glutathione peroxidase since McClelland *et al.* taught that the adenoviral vectors were useful for the purpose disclosed in Ohya *et al.* and were advantageous for such a purpose.

(Office Action, page 4.) Applicants point out, however, that the Office previously admitted that McClelland is deficient because McClelland "does not teach that glutathione peroxidase is a protein of interest." (Office Action dated January 21, 1998, page 21.) Accordingly, Applicants contend that McClelland could not possibly specifically teach that McClelland's adenoviral vectors are useful for Ohya's purpose of transfecting cultured mammalian cells for the production of the glutathione peroxidase. At most, the disclosure of McClelland, with the recitation "DNA sequences encoding therapeutic agents," only provides "general guidance as to the particular form of the claimed invention." (*In re O'Farrell*, 7 U.S.P.Q.2d 1673 at 1681 (Fed. Cir. 1988 (emphasis added).) Further, there is nothing in Ohya that would provide motivation to one of ordinary skill in the art to combine the Ohya's method of transfecting cultured mammalian cells for the production of the glutathione

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

peroxidase with McClelland's adenoviral vectors. Neither McClelland, Ohya, or the combination thereof provide evidence of the desirability leading one of ordinary skill in the art to formulate a recombinant adenovirus comprising a nucleic acid encoding a human glutathione peroxidase. As in *O'Farrell*, the Office is employing an impermissible "obvious to try" standard of in suggesting that it would have been obvious to combine the Ohya's plasmid encoding a glutathione peroxidase with McClelland's recombinant adenoviral vector.

As the use of a recombinant adenovirus that comprises a nucleic acid encoding a human glutathione peroxidase would be, at best, "obvious to try" or "obvious to experiment," in the claimed invention, there is no motivation to combine the cited references. Therefore the rejection is improper, and Applicants respectfully request reconsideration and withdrawal of the rejection.

SUMMARY

In view of the above remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: _____
Charles D. Niebylski
Reg. No. 46,116
(202) 408-4128

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FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com